Some aspects of radical cascade and relay reactions

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The ability to create carbon–carbon bonds is at the heart of organic synthesis. Radical processes are particularly apt at creating such bonds, especially in cascade or relay sequences where more than one bond is formed, allowing for a rapid assembly of complex structures. In the present brief overview, examples taken from the authors’ laboratory will serve to illustrate the strategic impact of radical-based approaches on synthetic planning. Transformations involving nitrogen-centred radicals, electron transfer from metallic nickel and the reversible degenerative exchange of xanthates will be presented and discussed. The last method has proved to be a particularly powerful tool for the intermolecular creation of carbon–carbon bonds by radical additions even to unactivated alkenes. Various functional groups can be brought into the same molecule in a convergent manner and made to react together in order to further increase the structural complexity. One important benefit of this chemistry is the so-called RAFT/MADIX technology for the manufacture of block copolymers of almost any desired architecture.

1. Introduction

The efficient formation of carbon–carbon bonds is at the heart of organic synthesis and shapes the overall strategies designed to construct given molecular architectures. Reaction sequences that lead to the simultaneous or consecutive formation of several new carbon–carbon bonds are particularly appealing since they can shorten considerably the synthetic path to complex scaffolds [1]. Not surprisingly, much effort has been devoted to the development of tandem, cascade and relay processes using all types of reactive intermediates. Spectacular cationic cascades of polyolefins imitating Nature’s squalene cyclases have been used in routes to terpenes and steroids and, more recently, elegant organocatalytic sequences have been marshalled to...
address problems in total synthesis [2,3]. The selective electrophilic activation of alkenes and allenes with gold complexes has seen a dramatic boom in recent times [4]. Combinations of anionic processes such as conjugate additions with alkylations or aldol reactions have also been used to great effect. Transition-metal-catalysed sequential transformations that result in multiple bond formation have been harnessed in almost every conceivable way [5]. Examples include the Pauson–Khand reaction [6], the powerful metathesis reaction [7], the Heck coupling and numerous related reactions involving palladium complexes [8]. Many elegant cascades of pericyclic reactions have been described and several have been incorporated in the total synthesis of natural products [9]. Sequences starting with carbenes (or carbenoids) and culminating with dipolar cycloadditions have proved especially impressive in attaining complicated frameworks [10].

Of all the reactive intermediates, radicals occupy a privileged position in terms of the facility to create new carbon–carbon (and carbon–heteroatom) bonds [11]. The reason for this is that the addition of a radical to an alkene leads to another radical which can undergo a second addition and so on and so forth. An extreme example is found in polymerizations, where hundreds if not thousands of carbon–carbon bonds are created from one initial radical. In the present account, examples of radical cascades and relay reactions involving radicals studied in the authors’ laboratory will be presented and discussed briefly. These transformations have been classed into four types: (i) sequences of intramolecular reactions; (ii) intramolecular–intermolecular combinations; (iii) intermolecular–intramolecular combinations; and (iv) intermolecular–intermolecular combinations. In one final section, the synthesis of block copolymers using what has become known as the RAFT/MADIX technology will be succinctly described.

2. Sequences of intramolecular reactions

There are literally hundreds of reported cascades involving intramolecular radical sequences. Many are spectacular transformations, from Breslow’s landmark radical version of the squalene-type cationic polycyclizations [12] to Curran’s elegant and probably still the shortest synthesis of hirsutene [13]. They tend to be the easiest to implement, since the key steps are unimolecular processes that are not affected by dilution, in contrast to most unwanted side reactions which are usually bimolecular (e.g. the ubiquitous premature abstraction of a hydrogen atom from tri-n-butylstannane). There is, however, a price to pay in that access to the precursor may sometimes be lengthy.

As part of our research programme related to the development of new, practical methods for the generation of nitrogen-centred radicals [14], we devised sequences allowing the construction of the pyrrolizidine and indolizidine backbones 3 and 5 found in many alkaloid families, as well as the rarer perhydroazaazulenone structure 7 present in certain natural substances such as the stemona alkaloids [15]. Our approach, which relies on our development of hydroxamate esters as convenient sources of amidyl radicals, is summarized in scheme 1. Thus, the amidyl radical derived from hydroxamate 1 first undergoes a rapid 5-exo ring closure to the alkene located on the main backbone to give intermediate radical 2, and this is followed by a second cyclization, the nature of which varies with the value of n and substituent X. For n = 1 and X = H, a second 5-exo ring closure provides indolizidine 4, where the chlorine can now be reductively removed by the stannane. The success of this sequence hinges on the inertness of vinylic chlorides towards stannyl radicals, thus allowing it to exert its directing effect [16]. Once the desired cyclization has taken place, the chloride in 4 is now aliphatic and can be reductively removed by the stannane. This difference in reactivity is simply a reflection of the increased difficulty in generating the much less stable vinylic radical in comparison with an aliphatic radical. Extending the side-chain by one more carbon whilst keeping the chlorine, as in 1 (n = 2; X = Cl), results in the formation of perhydroazaazulenone 7 through a 7-exo closure and
Scheme 1. General routes to pyrrolizidines, indolizidines and perhydroazaazulenes [15].

Scheme 2. A short synthesis of (±)-aspidospermidine [17].

reductive dechlorination of intermediate 6. This framework is a conserved structural element in the stemona family of alkaloids.

This strategy was successfully applied in short syntheses of (±)-aspidospermidine 11 [17] and 13-deoxyserratine 17 [18]. For the former, the requisite precursor 9 was readily secured by an alkylative Birch reduction of benzoate 8, which in turn furnished key tricyclic intermediate 10 through the radical cascade sequence (scheme 2). The synthesis was completed in four steps by adopting the final stages described previously by Stork & Dolfini [19].

The second target, 13-deoxyserratine 17, is more challenging. Indeed, the presence of two adjacent quaternary centres at C(4) and C(12) proved to be a significant hurdle in earlier routes to this family of natural products. It turns out that the radical cascade starting with an amidyl radical allows the simultaneous creation of both quaternary centres with the correct relative stereochemistry (scheme 3). The requisite precursor 15 was assembled by an efficient sequence starting from hex-5-yn-2-one 12. The compound was first elongated at both extremities in two easy steps and the resulting enyne 13 subjected to the formidable Pauson–Khand reaction to give bicyclic intermediate 14. The side-chain was then processed in a standard fashion to furnish the desired hydroxamate precursor 15. We were pleased to find that exposure to two equivalents of stannane in refluxing trifluorotoluene gave rise to the expected tetracyclic product 16 with complete control of the relative stereochemistry of the two adjacent quaternary centres and acceptable efficiency, in view of the large number of elementary steps involved. In this transformation, ACCN (1,1′-azobis(cyclohexanecarbonitrile)) was used as the initiator instead
of the ubiquitous AIBN, the half-life which is too short at the reflux temperature (102°C) of trifluorotoluene. Protection of the ketone as an enol silyl ether allowed the chemoselective reduction of the lactam and, finally, deprotection with tetrabutylammonium fluoride released both the tertiary alcohol and the ketone functions. Thus, the target 13-deoxyserratine 17 could be obtained in 10 steps and about 12% overall yield. This represents a considerable improvement on previous more classic approaches.
The intramolecular combinations need not involve only cyclization reactions. For the total synthesis of \((-\)-dendrobine 24 from \((+)-trans\)-verbenol 18, we exploited the cyclization of a carbamoyl radical generated from hydroxamate precursor 19 in combination with a concomitant ring opening of the cyclobutane ring to give bicyclic carbamate 20 (scheme 4) [20]. This compound was not isolated, but cleaved with potassium hydroxide into aminoalcohol 21 containing three of the seven adjacent chiral centres in dendrobine (six of them around the central cyclohexane!). Aminoalcohol 21 was then propargylated and acetylated to give enyne 22, and this was converted by the Pauson–Khand reaction and catalytic reduction into tricyclic key intermediate 23. Transformation of the latter into \((-\)-dendrobine 24 was finally completed in eight steps.

The construction of \((\pm\)-fortucine 29 took advantage of a different amidyl radical precursor and relied on a 5-exo cyclization followed by ring closure onto an aromatic nucleus, as pictured in scheme 5 [21]. Monoprotected benzoquinone 25 was processed into key dithio semicarbazone intermediate 26 in high overall yield. Heating this compound with a stoichiometric quantity of lauroyl peroxide resulted in the formation of tetracyclic lactam 28 in 60% yield. The undecyl radical arising from the thermolysis of lauroyl peroxide attacks the radicophilic thiocarbonyl group in hydrazide 26 and causes the rupture of the relatively weak nitrogen–nitrogen bond. Closure onto the aromatic ring leads to stabilized cyclohexadienyl radical 27, which is oxidized to the corresponding cationic species by electron transfer to the peroxide. Loss of a proton restores the temporarily lost aromaticity and furnishes compound 28 possessing the complete carbon framework of fortucine. The synthesis of \((\pm\)-fortucine 29 required a total of 11 steps and proceeded in about 10% overall yield.

Scheme 5. The total synthesis of \((\pm\)-fortucine [21].
3. Intramolecular–intermolecular combinations

A faster, more convergent access to structural intricacy can be secured by incorporating one or more intermolecular steps in the cascade. In this manner, more atoms are added to the initial skeleton with the corresponding increase in the molecular complexity. One such example is the sequence starting from phenylsulfenylimine 30 derived from Δ²-(+)-carene and displayed in scheme 6 [22]. The iminyl radical generated by attack of the stannyl radical on the sulfur atom undergoes ring opening, triggering in turn the fragmentation of the cyclopropane to give tertiary radical 31. In the presence of methyl acrylate as the electrophilic external trap, this electron-rich species can be captured to give bicyclic structure 32 by addition, ring closure and quenching of the last radical by the stannane.

The second sequence in the same scheme illustrates the interception by an internal alkene of an iminyl radical 34, produced from the corresponding oxime xanthate 33 [23]. The resulting cyclized radical 35 is in turn captured by phenyl vinyl sulfone to give adduct radical 36 that finally propagates the chain by reacting with the starting xanthate 33 and furnishing densely functionalized product 37. This highly efficient chain reaction is initiated by irradiation with visible light. In the absence of an external trap, irradiation converts the starting xanthate 33 into pyrrolenine 38. In this case, the last propagation step is the reaction of radical 35 with xanthate 33. By performing the irradiation in bromotrichloromethane, the reaction leads to bromide 39 by a bromine atom transfer from the solvent to radical 35.

The ability to transfer a heteroatom or a group of atoms can be used in different contexts. One interesting system is the generation of radicals by electron transfer from metallic nickel. We found that plain nickel powder is capable of transferring a single electron to a trichloroacetamide such as 40 (among other reducible groups) to generate the corresponding radical anion, which collapses to produce a chloride anion and dichloromethyl radical 41 (scheme 7) [24]. Under the reaction conditions, the latter is sufficiently long-lived to allow its interception by a well-positioned alkene, and the resulting cyclized radical captured by a trap incorporated into the medium. Thus, bromine atom transfer from bromotrichloromethane gives rise to bromolactam 42, whereas selenide 43 is obtained in high yield in the presence of diphenyl diselenide. Capture of cyclized radical intermediate 41 with TEMPO or with ethyl cyanoformate furnishes, respectively, hydroxylamine 44 or ketoester 45, the latter by hydrolysis of the intermediate imine (not shown). Finally, we found that the mild reducing Ni/AcOH system is compatible with the presence of cupric acetate, a weak oxidant but fast radical trap [25]. This allows the capture and conversion of radical 41 into alkene 46 in good yield. In all of these transformations, the dichlorolactam motif in the products is not further reduced, testifying to the remarkable mildness and chemoselectivity of this unusual reducing reagent.

Another useful association is the cyclization of a xanthate with an allylation involving allyl ethyl sulfone. An example is provided in scheme 8 starting with xanthate 47 [26]. Radical exchange of the xanthate group leads to radical 48, which undergoes ring closure into lactam 49. This radical can and does exchange a xanthate group by reacting with the starting material 47, but this is a reversible process (more on the remarkable properties of the xanthate transfer in the next section). Ultimately, radical 49 participates in an addition fragmentation with allyl ethyl sulfone to give the final product 50, where two new carbon–carbon bonds have been formed with complete control of the relative stereochemistry. The ethylsulfonyl radical released in the process extrudes a molecule of sulfur dioxide to give an ethyl radical capable of propagating the chain.

4. Intermolecular–intramolecular combinations

Convergence is obviously also achieved by inverting the order of the intramolecular and intermolecular processes. A dramatic example is displayed in scheme 9, hinging on the Barton decarboxylation reaction whereby a cyclization is intercalated between two intermolecular additions [27]. Starting with hydroxamate 51 (also called a Barton ester) and phenyl vinyl sulfone as the external trap, the sequence leads to bicyclo[3.3.0]octane structure 53 where three...
new carbon–carbon bonds and one carbon–sulfur have been created. The last propagation step involves the reaction of radical 52 with the starting hydroxamate 51. This step is much faster than further addition of electron-poor radical 52 to the electrophilic phenyl vinyl sulfone. Taking advantage of this polar mismatch obviates the formation of unwanted oligomers and allows a clean control of the cascade. Under the same experimental conditions, Barton ester 54 gives rise to bicyclo[2.2.1]heptane structure 55. Furthermore, the presence of the pyridylthio moiety in the product allows an easy differentiation between the two phenylsulfone groups. For instance, only the side-chain sulfone is replaced by a methyl group upon exposure to trimethylaluminium, furnishing compound 56 in high yield [28]. Many different frameworks may be constructed by simply modifying the initial Barton ester and varying the nature of the electrophilic olefinic trap.

In reactions involving triorganotin hydrides or the Barton decarboxylation, the external olefinic trap has to be sufficiently reactive (e.g. methyl acrylate or phenyl vinyl sulfone in scheme 6 and scheme 9) to be able to compete with the fast hydrogen abstraction from the stannane or the addition fragmentation on the Barton ester. This introduces severe limitations in terms of scope. Indeed, intermolecular radical additions to unactivated alkenes are difficult to accomplish with most methods because they are normally unable to compete against the background reactions. To quote D. Curran, a pioneer in the use of radical cascades in synthesis, ‘The full potential of bimolecular radical carbon–carbon bond forming reactions has yet to be realized’ [29]. This gap in synthesis has now been largely filled by a reaction we discovered some time ago. It is based on the degenerative xanthate transfer depicted in greatly simplified form in scheme 10 [30,31].

This process has some unique features. It allows particularly the reversible storage of radicals under a relatively non-reactive form and lowers the absolute concentration of all active radicals while simultaneously regulating their relative concentrations. It thus fulfils two seemingly
contradictory requirements, namely the ability to increase considerably the lifetime of the radicals, even in a concentrated medium (important to promote bimolecular reactions), while at the same time limiting the extremely fast, diffusion-controlled, but undesirable, radical–radical interactions. For a more detailed discussion of the mechanism, the reader is directed to [29,30]. For the purposes of the present overview, suffice it to say that the reaction of radical $R^\bullet$ with its precursor $57$ to give intermediate $58$ (path A) is reversible and degenerate and, therefore, not in
Scheme 9. Radical cascades with Barton esters [27,28].

Scheme 10. The addition of xanthates to alkenes and an example [30–32].
Scheme 11. The formation of a tetrasubstituted allene en route to a tricyclic structure [33].

The ability to add to unactivated alkenes and the general tolerance of radical reactions to polar functional groups open up infinite possibilities for the convergent construction of complex scaffolds. Since its discovery, at least 2000 additions employing over 200 different xanthates have been reported. One example of sequential intermolecular and intramolecular reactions pitting together β-pinene 61 and bis-xanthate 62 is shown in scheme 10 [32]. The first step involves radical addition to the exocyclic alkene with concomitant opening of the cyclobutane ring to give intermediate 63. This is followed by a 6-endo ring closure mediated by the second xanthate group to give the cis-decalin derivative 64 as a single stereoisomer.

In scheme 11, the addition of malonyl xanthate 66 to enyne 65 leads to a propargylic radical intermediate (not shown), which undergoes ring closure to the cyclohexene motif to produce tetrasubstituted allene 67 [33]. In this case, the allenyl acetate motif can be solvolysed into enone 68 by heating in aqueous acetic acid and converted into tricyclic compound 69 by an internal Michael addition induced by exposure to base. In this sequence, the stereochemistry of the chiral centre indicated with an asterisk in starting enyne 65 has been parlayed into three other chiral centres in the final product (asterisked carbons). The last asymmetric centre adjacent to the ketone and bearing a methyl group is not controlled but can be corrected through the enol or the enolate.

Another versatile route to polycyclic frameworks associates the intermolecular radical addition and cyclization with the Claisen rearrangement and a Robinson-type annulation. One such example is displayed in scheme 12 [34]. Thus, vinyl enol ether 71 derived from allylic alcohol 70 is readily converted into enone 72 in three steps including the key Claisen rearrangement, which transfers the stereochemical information present in alcohol 70 to the quaternary centre in enone 72. Addition cyclization of xanthate 73 gives rise to bicyclic ketone 74 that is well suited to a Robinson-type annulation after reductive removal of the xanthate to give triquinane 75. The yield in parentheses is based on recovered starting material (b.r.s.m.).

The ring-closure step need not involve addition to an internal alkene. Any group capable of capturing a radical can be harnessed and exploited to provide a variety of synthetic variations. In the sequence depicted in scheme 13, the internal radical trap is an acylphosphonate [35]. Thus, addition of xanthate 77 to the terminal olefin in substrate 76 leads initially to radical 78. This is rapidly intercepted by the acyl group to give highly reactive alkoxy radical 79, which immediately
Scheme 12. A convergent route to a triquinane [34].

Scheme 13. Example of a synthesis of a 1,5-diketone and the corresponding pyridine [35].

evolves into dihydroquinolone 80 by expelling a phosphonyl radical. The 1,5-disposition of the two ketones in this compound allows its conversion into pyridine 81 by treatment with ammonium acetate in acetic acid.

The formation of pyridine 81 is just one example of a heteroaromatic structure that may be of interest to medicinal chemists. Nitrogen heterocycles in general dominate the fields of medicinal chemistry and agrochemicals [36]. By associating an intermolecular radical addition with a ring closure onto an aromatic or a heteroaromatic nucleus, various privileged nitrogen-containing aromatic scaffolds can be readily assembled [37]. The second step requires the use of a stoichiometric quantity of the peroxide, which is needed to oxidize the intermediate cyclic adduct radical into the corresponding cation and thus restore the temporarily lost aromaticity (cf. the
Scheme 14. Synthesis of a difluoromethyl-substituted indoline and indole [38].

Scheme 15. Synthesis of an indoline substituted in the 2-position [41].

conversion of intermediate 27 into 28 in scheme 5). An example of the synthesis of an indoline and an indole is provided in scheme 14 [38]. In this case, the addition and cyclization to N-allyl-N-mesyl-p-bromoaniline 82 are conducted in one pot to give difluoromethyl indoline 83. Heating this compound with DBU leads to indole 85 by elimination of a chloride, migration of the alkene into the ring in the intermediate 84, and loss of the mesyl protecting group. It is possible to isolate olefin 84, if so desired, by operating below 40°C. The facility with which fluorinated groups can be introduced using xanthate chemistry is also worthy of note [39]. It is indeed estimated that 25–30% of all drugs and agrochemicals contain at least one fluorine atom [40].

The above approach to indolines and indoles furnishes derivatives substituted on position C-3. It proved possible to conceive a route leading to indolines substituted on C-2 by taking advantage of a chelotropic elimination of sulfur dioxide from addition-cyclization products such as 87, obtained by reaction of a xanthate with N-vinylsulfanilide 86 (scheme 15) [41]. Thermolysis of compound 87 furnishes iminoquinone methide 88, in equilibrium with its geometrical isomer 89. The latter is rapidly converted into aniline 90 by a 1,5 sigmatropic hydrogen shift. Exposure of this compound to base establishes an equilibrium with its isomer 91, whereby the olefin is now
Scheme 16. Examples of a polycyclic azetine and a benzazepinone [42,43].

conjugated with the nitrile group and, therefore, electrophilic and susceptible to conjugate attack by the aniline to give indoline 92.

Terminal alkenes are generally the best substrates for the radical addition. Internal alkenes react more slowly, with complications due to low regioselectivity and abstraction of allylic hydrogens. There are, however, certain special internal alkenes that do not suffer from these drawbacks. Azetines belong to such a class. Thus, as shown in scheme 16, addition of xanthate 93 to Boc-protected azetine affords adduct 94 cleanly [42]. Further treatment with stoichiometric amounts of lauroyl peroxide induces cyclization to the pyridine ring to give tricyclic compound 95 belonging to a novel structural family.

An almost unique feature of the xanthate radical chemistry is its ability to fuse five-, six- and even seven-membered rings to aromatic nuclei. An example of the last case is displayed in the lower part of scheme 16 involving xanthate 96 formed by radical addition to glucosamine derivative 96 [43]. Exposure to peroxide regenerates intermediate radical 98 which cyclizes onto the aryl ring with concomitant cleavage of the relatively weak nitrogen–oxygen bond. This sequence provides benzazepinone 99 unsubstituted on the nitrogen atom. Structures such as 95 and 99 would be very tedious to construct by other pathways.

A conceptually similar approach to N-unsubstituted benzazepinones relies on the fragmentation of a nitrogen–sulfur bond in sulfonanilides. This is illustrated by the synthesis of benzazepinones 103 and 106 from xanthates 100 and 104 pictured in scheme 17 [44]. The cyclization of the respective intermediate adducts 101 and 105 requires higher temperature and...
the use of di-\(t\)-butyl peroxide, instead of the ubiquitous lauroyl peroxide. Despite the harsher conditions, benzazepinones with a variety of substituents can be prepared by this route. In the case of benzazepinone 106, deprotection of the primary amine with TFA and neutralization with triethylamine triggers a trans-amidification, whereby the cyclic anilide is replaced by the more stable pyridone 107. While not necessary for the radical cyclization, the tolerance for bromine or iodine on the aromatic ring in all of these compounds provides a handle for further diversification by numerous transition-metal-catalysed couplings.

The ability to accomplish the radical equivalent of an intramolecular Friedel–Crafts reaction associated with a prior intermolecular addition to an unactivated alkene can result in a significant simplification of synthetic schemes. Two illustrations are presented in scheme 18 and scheme 19. The first concerns the total synthesis of (±)-10-norparvulenone 113, a natural product isolated at the turn of the century from Microsphaeropsis sp. and claimed to be a promising anti-influenza virus antibiotic [49]. The requisite xanthate 109 is readily obtained from 3-methoxyphenol 108 and its addition to vinyl pivalate furnishes adduct 110 in good yield [45]. Ring closure into tetralone 111 is effected by further exposure to lauroyl peroxide. Interestingly, both radical reactions can be performed despite the presence of a naked phenol. Phenols are known, and indeed in some cases used, as radical chain inhibitors [50]. In the present case, hydrogen bonding with
the ketone carbonyl decreases considerably its hydrogen-donating ability and at the same time biases the radical derived from adduct 110 in a conformation propitious for cyclization onto the aromatic ring. The pivalate group proved to be robust enough to allow Lewis acid-mediated introduction of the formyl group to give aldehyde 112 [46]. Finally, selective reduction with sodium cyanoborohydride and saponification afforded the target molecule.

The second example corresponds to a formal synthesis of (±)-mersicarpine 118, an indole alkaloid isolated from the Kopsia species of flowering plants found mainly in South East Asia (scheme 19) [51]. In this case, the addition cyclization of xanthate 114 with alkene 115 was performed in one pot [47]. The presence of the ester group on the indole nucleus was needed to improve the cyclization step, but its electron-withdrawing effect diminished the efficiency of the final oxidation and caused the accumulation of variable amounts of the indoline (not
shown) corresponding to indole 116. Manganese dioxide was, therefore, added at the end of the reaction to oxidize the remaining indoline and complete the aromatization. It is worth pointing out the ease with which the quaternary centre is generated in the process. Removal of the tert-butyl carboxylate group was accomplished by heating with trifluoroacetic acid in toluene. This caused the simultaneous deprotection of the terminal amine. The Boc group had, therefore, to be reinstalled to give 117, an advanced intermediate in the first total synthesis of mersicarpine by Kerr and co-workers [48].

5. Intermolecular–intermolecular combinations

Combining intermolecular reactions is the fastest and most efficient way to attain complexity as well as diversity. The ability to string together different and separate building blocks allows highly convergent synthetic plans to be conceived and implemented. In this respect, the degenerate addition transfer of xanthates is particularly efficient. Not only are the pools of starting xanthates and alkenes sufficiently large to give rise to an almost infinite number of combinations, but the product of the addition is itself a xanthate and, therefore, a potential starting point for another intermolecular radical addition. The application of this property to the manufacture of block polymers will be described in the following section. For the synthesis of ‘small’ molecules, the successive addition to different alkenes is possible if the reaction components are selected in such a way that the adduct radical 59 is less stable than starting radical R+ (scheme 10). In this manner, the equilibrium favours product 60 and the formation of oligomers by further additions of radical 59 to the alkene is curtailed. This simplified rule is based solely on the thermodynamic stabilities of the intermediate radicals and does not take into account possible polar factors that could alter the kinetics of the process. In the sequence in scheme 20, where the densely functionalized and reasonably complex structure 122 is expediently assembled by stitching together one xanthate and three different olefins under essentially identical experimental conditions, this constraint has been respected [52]. Thus, addition of xanthate 119 to N-vinyl phthalimide furnishes adduct 120, which in turn is added to vinylene carbonate and the resulting adduct 121 finally added to allyl trimethylsilane.

Perhaps less spectacular, but synthetically more useful, is the sequence outlined in scheme 21. It consists in performing the addition of the acetone-derived xanthate to vinyl trimethylsilane and exploiting the presence of the xanthate in the corresponding adduct 123 to accomplish a second radical reaction with ethyl dichlorovinylsulfone as the external trap [53]. This operation results in the replacement of the xanthate group with a dichlorovinyl motif through a radical addition fragmentation and expulsion of an ethylsulfonyl radical (see scheme 8) [55]. The product, 124, has an interesting combination of functional groups that can be exploited in a number of ways. For example, treatment with magnesium in methanol generates the ketyl radical from the ketone, which immediately adds to the dichloro-olefin in a 5-endo fashion to furnish cyclopentanol 125 as a 4:1 mixture of epimers [54]. Alternatively, the ketone can be protected as ketal 126 and the dichlorovinyl moiety converted into lithium acetylide 127 with BuLi and quenched with cyclohexanone to give propargyl silane 128 through the classical Corey–Fuchs reaction [53,56]. The propargyl silane motif is readily and cleanly transformed into allene 129 by the action of fluoride anion. Prior conversion of the alcohol into a leaving group and exposure to fluoride would lead to triene 130. One literature report indicates that such cumulenes are indeed accessible by this approach.

The alkylation of ketone enolates is a classical and fundamental transformation described to students in their very first organic chemistry course, yet it is a reaction that is rarely trivial to accomplish in practice [57]. Complications rapidly arise due to the formation of regioisomers (including C- versus O-alkylation), multiple alkylations, self-condensations, etc. Furthermore, yields decrease sharply with even a modest increase in the size and complexity of the alkylating agent, unless a special feature is present that enhances significantly the reactivity, as in allylic and benzylic derivatives. By using the radical chemistry of xanthates, many of these problems disappear. For instance, the formation of adduct 123 in scheme 21 can be viewed as a clean,
Scheme 20. Three successive radical additions [52].

regioselective monoalkylation of acetone with vinyl trimethylsilane acting as the alkylating agent. Indeed, much more complex unsymmetrical ketones can be accessed by a two-directional elongation exploiting the small difference in radical stability between primary and secondary radicals.

The principle is outlined in scheme 22 [58]. Bis-xanthate 131 can and does give rise to both radicals 132 and 133, but the very rapid exchange of the xanthate group (most likely an intramolecular process in this case) creates an equilibrium between the two radicals which greatly favours the more substituted radical. A simple alkyl group will provide 3–4 kcal mol$^{-1}$ extra stabilization resulting in at least a hundred-fold greater concentration of radical 132 over that of 133 at equilibrium. In the presence of the alkene as the limiting reagent, adduct 134 will, therefore, be formed regioselectively. For the same reasons, this new bis-xanthate will in turn react regioselectively with a second alkene to furnish ketone 135. Reductive removal of both xanthates in this adduct, finally, provides unsymmetrical ketone 136, where two new carbon–carbon bonds on either side of the carbonyl group have been created.

The feasibility of this strategy was readily verified, as illustrated by the reaction of bis-xanthate 131a, a compound trivially made by reaction of 1,3-dibromo-2-butanone with potassium O-ethyl xanthate in acetone (scheme 23) [58]. Addition with N-allyl-phthalimide as the limiting component indeed afforded adduct 134a regioselectively and in good yield. A second addition of this new bis-xanthate to allyl acetate also occurred efficiently and regioselectively to give compound 135a. Finally, reduction with hypophosphorous acid furnished the desired unsymmetrical ketone 136a in good overall yield.

This approach proved quite general and could be extended to many other ketone derivatives, a number of which are displayed in figure 1. The three yields given for each product correspond to the first and second radical additions and to the final reduction, respectively. Examples 136b–h all start with the same bis-xanthate 131a. Example 136i demonstrates the tolerance of the radical addition to the presence of a relatively bulky isopropyl group. In view of the ubiquity of both methyl and isopropyl groups in terpenes, these sequences could find interesting synthetic applications in this area. Examples 136j–p illustrate the possibility of another polar group being present in the starting bis-xanthate, such as an ester or a phthalimide. The last four products in this group represent the formal distal dialkylation of ethyl acetoacetate, a transformation commonly accomplished through the dianion under strongly basic conditions.
Scheme 21. Formation of cyclopentanols and allenes [53,54].

The present radical-based route is a powerful alternative to enolate chemistry. Indeed, access to most of the structures in figure 1 by other more classic approaches would have required many more steps. The remarkable tolerance of radicals for numerous functional groups, and especially polar groups, allows the bringing together of a large number of different entities that could then be made to react with each other by a suitable change in the experimental conditions (pH, temperature, etc.) or through the influence of an external agent. In compound 136b, for example, addition of base would have caused the phosphonate to condense with the ketone to give a cyclohexene derivative.

6. Controlled radical polymerization

As stated in the Introduction, polymerizations represent perhaps the ultimate in terms of cascade efficiency. Radicals are particularly apt in this area and the most common industrial polymers (polystyrene, synthetic rubber, PVC, polyacrylates and polymethacrylates, polyvinyl alcohol, etc.) are manufactured by radical processes on a huge scale [59]. The classical radical polymerization, depicted at the top of scheme 24, leads to what are called dead polymers because they cannot...
be easily further modified in a controlled manner. In these processes, the polymerization for a given chain ends when two macroradicals 137 either couple to give dimer 138 or disproportionate into the reduced and oxidized radicals 139 and 140. This results in a rather broad distribution of molecular weights, the so-called polydispersity index.

The situation becomes completely different if the polymerization is performed in the presence of a small amount of a suitable xanthate 141 (Z = OEt) or, more generally, a dithiocarbonyl derivative such as a dithioester (Z = Ph) or a trithiocarbonate (Z = SR) [60–62]. The polymerization, detailed in the lower half of scheme 24, starts with the ‘normal’ addition to the monomer to give the usual adduct but, since the adduct radical can be easily regenerated, further additions and exchanges of the dithiocarbonyl derivative take place continuously until the monomer is depleted. This leads to polymer 142 with a narrow polydispersity index because all the chains can keep growing as long as there is monomer present (the shorter chains are slightly more mobile and grow slightly faster). The polymer strands are further capped by the
Figure 1. Examples of unsymmetrical ketones [58].

dithiocarbonyl group and can, therefore, act as the starting material for another polymerization with a different monomer to give block copolymer 143. And the process can be pursued if so desired. This so-called RAFT/MADIX technology has proved extremely powerful, as can be judged from the large number of publications and patents related to it [63]. Almost any desired polymeric architecture can be assembled and the process is easily implemented on an industrial scale. Indeed at least two block copolymers, Rhodibloc® (Solvay) and Asteric® (Lubrizol), are now in commercial production.
The discovery of the xanthate transfer in the mid-1980s [64] paved the way for the development of the RAFT/MADIX-controlled radical polymerization technology. Another consequence in the polymer field is the ability to profoundly modify existing commercial polymers. One example is depicted in scheme 25, where commercial poly-1,2-butadiene 144 is converted into multiple addition product 145 (cyclopentane rings can also be occasionally formed by 5-exo cyclizations but are not shown for simplicity) [52]. Deprotection would lead to a polyaminothiol polymer 146, which could have various interesting applications, such as in the extraction and recovery of toxic or precious heavy metals. In principle, several xanthates could be added simultaneously, thus giving rise to a new polymer decorated with a plethora of different functional groups.
7. Concluding remarks

The surge in the applications of radical reactions in organic synthesis that took place in the 1980s and early 1990s relied heavily on the chemistry of organotin reagents. Numerous cascades were devised and in many cases applied to the total synthesis of natural products of almost all structural types. The focus has somewhat shifted in more recent times to tin-free methods [65]. Much progress has been accomplished in the use of organoboranes [66,67] and in transition-metal-mediated radical transformations, especially in redox and photoredox reactions [68,69]. Their implication in cascade processes will gain in importance as their use becomes more widespread. Many of the transition-metal complexes and intermediates involved are in fact persistent radicals and the elementary steps in which they are implicated are under the control of the so-called persistent radical effect or the Fischer–Ingold effect [70,71], a profound concept with far-reaching consequences, but the importance of which is still vastly underestimated. This is an unfortunate state of affairs that is attributable in large measure to the absence of fully fledged courses on radical chemistry in most universities, even top-tier ones. It is hoped that the situation will eventually change and that radicals will find a place in the curriculum for chemistry students commensurate with their importance.

For our part, although we have developed a few organotin-based methods, particularly in relation to the generation and capture of nitrogen-centred radicals, we have devoted much of our efforts to the design and study of tin-free radical processes, as the examples in this brief account have highlighted. In this respect, the thiocarbonyl group has played a major role, especially as concerns the degenerative exchange of xanthate. This technology, which has its origins in the landmark Barton–McCombie deoxygenation [72], has proved to be remarkably powerful and particularly adapted for cascade and relay sequences. Indeed, despite much work, only a small fraction of its wide possibilities has been explored so far.

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